



SEQUENCE LISTING

<110> WOULFE, SUSAN L.
JAIN, RITA
BURR, AIMEE

<120> ENGINEERED FAB' FRAGMENT ANTI-TUMOR
NECROSIS FACTOR ALPHA.IN COMBINATION WITH DISEASE MODIFYING
ANTI-RHEUMATIC DRUGS

<130> 122294-1010

<140> US/10/728,420

<141> 2003-12-05

<150> US 60/431,053

<151> 2002-12-05

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<223> Mouse monoclonal antibody hTNF40 CDRH1

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Asp Tyr Gly Met Asn

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<223> Mouse monoclonal antibody hTNF40/human hybrid CDRH2

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Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Ala Asp Ser Val Lys

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Gly

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Gly Tyr Arg Ser Tyr Ala Met Asp Tyr
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Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
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Ser Ala Ser Phe Leu Tyr Ser
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Gln Gln Tyr Asn Ile Tyr Pro Leu Thr
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<222> (1)...(321)
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 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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 gac cgg gtc acc atc act tgt aaa gcc agt cag aac gta ggt act aac 96
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
 20 25 30
 gta gcc tgg tat cag caa aaa cca ggt aaa gcc cca aaa gcc ctc atc 144
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
 35 40 45
 tac agt gcc tct ttc ctc tat agt ggt gta cca tac agg ttc agc gga 192
 Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Tyr Arg Phe Ser Gly
 50 55 60
 tcc ggt agt ggt act gat ttc acc ctc acg atc agt agc ctc cag cca 240
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 gaa gat ttc gcc act tat tac tgt caa cag tat aac atc tac cca ctc 288
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Leu
 85 90 95
 aca ttc ggt cag ggt act aaa gta gaa atc aaa 321
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
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<222> (1)...(354)
<223> Synthetic gh3hTNF40.4

<223> Grafted Heavy Chain for Modified Fab

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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tca ctg aga ttg tcc tgt gct gca tct ggt tac gtc ttc aca gac tat 96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Val Phe Thr Asp Tyr
20 25 30

gga atg aat tgg gtt aga cag gcc ccg gga aag ggc ctg gaa tgg atg 144
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

ggt tgg att aat act tac att gga gag cct att tat gct gac agc gtc 192
Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Ala Asp Ser Val
50 55 60

aag ggc aga ttc acg ttc tct cta gac aca tcc aag tca aca gca tac 240
Lys Gly Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
65 70 75 80

ctc caa atg aat agc ctg aga gca gag gac acc gca gtg tac tat tgt 288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

gct aga gga tac aga tct tat gcc atg gac tac tgg ggc cag ggt acc 336
Ala Arg Gly Tyr Arg Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
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Leu Val Thr Val Ser Ser
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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys
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Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15
Asp Arg Val Ser Val Thr Cys
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<210> 85
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Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
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Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
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Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
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Gly Val Pro Tyr Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr
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Leu Thr Ile Ser Thr Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys
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Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
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Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
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<210> 91
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<400> 91
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
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<210> 92
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1 5 10 15
Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Val Phe Thr
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<210> 93
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<400> 93
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
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Arg Val Thr Ile Thr Arg Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
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Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
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Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe Leu Gln
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Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
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Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
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gac att gtg atg acc cag tct caa aaa ttc atg tcc aca tca gta gga 48
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
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gac agg gtc agc gtc acc tgc aag gcc agt cag aat gtg ggt act aat 96
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

gta gcc tgg tat caa cag aaa cca gga caa tct cct aaa gca ctg aat 144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Asn
35 40 45

tac tcg gca tcc ttc cta tat agt gga gtc cct tat cgc ttc aca ggc 192
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Tyr Arg Phe Thr Gly
50 55 60

agt gga tct ggg aca gat ttc act ctc acc atc agc act gtg cag tct 240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Thr Val Gln Ser
65 70 75 80

gaa gac ttg gca gag tat ttc tgt cag caa tat aac atc tat cct ctc 288
Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ile Tyr Pro Leu
85 90 95

acg ttc ggt gct ggg acc aag ctg gag ctg aaa cgt 324
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
100 105

<210> 100
<211> 354
<212> DNA
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<220>
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<222> (1)...(354)
<223> mouse hTNF40 heavy chain variable domain

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cag atc cag ttg gtg cag tct gga cct gag ctg aag aag cct gga gag 48
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

aca gtc aag atc tcc tgc aag gct tct gga tat gtt ttc aca gac tat 96
Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Val Phe Thr Asp Tyr
20 25 30

| | |
|---|-----|
| gga atg aat tgg gtg aag cag gct cca gga aag gct ttc aag tgg atg | 144 |
| Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Ala Phe Lys Trp Met | |
| 35 40 45 | |

| | |
|---|-----|
| ggc tgg ata aac acc tac att gga gag cca ata tat gtt gat gac ttc | 192 |
| Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Val Asp Asp Phe | |
| 50 55 60 | |

| | |
|---|-----|
| aag gga cga ttt gcc ttc tct ttg gaa acc tct gcc agc act gcc ttt | 240 |
| Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe | |
| 65 70 75 80 | |

| | |
|---|-----|
| ttg cag atc aac aac ctc aaa aat gag gac acg gct aca tat ttc tgt | 288 |
| Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys | |
| 85 90 95 | |

| | |
|---|-----|
| gca aga ggt tac cgg tcc tat gct atg gac tac tgg ggt caa gga acc | 336 |
| Ala Arg Gly Tyr Arg Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr | |
| 100 105 110 | |

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|-------------------------|-----|
| tca gtc acc gtc tct tca | 354 |
| Ser Val Thr Val Ser Ser | |
| 115 | |

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| cttggctctg acgtacgagt cagg | 84 |

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g agc tca cca gta aca aaa agt ttt aat aga gga gag tgt ta atg aag 48
Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Met Lys
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aag act gct ata gca att g 67
Lys Thr Ala Ile Ala Ile
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g agc tca cca gta aca aaa agt ttt aat aga ggg gag tgt taa 43
Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys *
1 5 10

a atg aag aag act gct ata gca att g 69
Met Lys Lys Thr Ala Ile Ala Ile
15 20

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<223> IGS cassette-3

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Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys *
1 5 10

ggaggaaaaa aaa atg aag aaa act gct ata gca att g 81
Met Lys Lys Thr Ala Ile Ala Ile
15 20

<210> 105
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<223> IGS cassette-4

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Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys *
1 5 10

cgaggattat ata atg aag aaa act gct ata gca att g 81
Met Lys Lys Thr Ala Ile Ala Ile
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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
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Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
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| Arg | Phe | Thr | Ile | Ser | Arg | Asp | Asn | Ser | Lys | Asn | Thr | Leu | Tyr | Leu | Gln |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Met | Asn | Ser | Leu | Arg | Ala | Glu | Asp | Thr | Ala | Val | Tyr | Tyr | Cys | Ala | Arg |
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<223> Synthetic CDP870 Light chain mature protein sequence

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| Asp | Ile | Gln | Met | Thr | Gln | Ser | Pro | Ser | Ser | Leu | Ser | Ala | Ser | Val | Gly |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Asp | Arg | Val | Thr | Ile | Thr | Cys | Lys | Ala | Ser | Gln | Asn | Val | Gly | Thr | Asn |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Val | Ala | Trp | Tyr | Gln | Gln | Lys | Pro | Gly | Lys | Ala | Pro | Lys | Ala | Leu | Ile |
| | | 35 | | | | | 40 | | | | 45 | | | | |
| Tyr | Ser | Ala | Ser | Phe | Leu | Tyr | Ser | Gly | Val | Pro | Tyr | Arg | Phe | Ser | Gly |
| | | 50 | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Ser | Gly | Thr | Asp | Phe | Thr | Leu | Thr | Ile | Ser | Ser | Leu | Gln | Pro |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Glu | Asp | Phe | Ala | Thr | Tyr | Tyr | Cys | Gln | Gln | Tyr | Asn | Ile | Tyr | Pro | Leu |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Thr | Phe | Gly | Gln | Gly | Thr | Lys | Val | Glu | Ile | Lys | Arg | Thr | Val | Ala | Ala |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Pro | Ser | Val | Phe | Ile | Phe | Pro | Pro | Ser | Asp | Glu | Gln | Leu | Lys | Ser | Gly |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Thr | Ala | Ser | Val | Val | Cys | Leu | Leu | Asn | Asn | Phe | Tyr | Pro | Arg | Glu | Ala |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Lys | Val | Gln | Trp | Lys | Val | Asp | Asn | Ala | Leu | Gln | Ser | Gly | Asn | Ser | Gln |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Glu | Ser | Val | Thr | Glu | Gln | Asp | Ser | Lys | Asp | Ser | Thr | Tyr | Ser | Leu | Ser |
| | | | 165 | | | | | | 170 | | | | | 175 | |
| Ser | Thr | Leu | Thr | Leu | Ser | Lys | Ala | Asp | Tyr | Glu | Lys | His | Lys | Val | Tyr |
| | | 180 | | | | | | 185 | | | | | 190 | | |
| Ala | Cys | Glu | Val | Thr | His | Gln | Gly | Leu | Ser | Ser | Pro | Val | Thr | Lys | Ser |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Phe | Asn | Arg | Gly | Glu | Cys | | | | | | | | | | |
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 <223> Synthetic CDP870 Heavy chain mature protein sequence

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| Glu | Val | Gln | Leu | Val | Glu | Ser | Gly | Gly | Gly | Leu | Val | Gln | Pro | Gly | Gly |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Ser | Leu | Arg | Leu | Ser | Cys | Ala | Ala | Ser | Gly | Tyr | Val | Phe | Thr | Asp | Tyr |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Gly | Met | Asn | Trp | Val | Arg | Gln | Ala | Pro | Gly | Lys | Gly | Leu | Glu | Trp | Met |
| | | | 35 | | | | 40 | | | | | 45 | | | |
| Gly | Trp | Ile | Asn | Thr | Tyr | Ile | Gly | Glu | Pro | Ile | Tyr | Ala | Asp | Ser | Val |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Lys | Gly | Arg | Phe | Thr | Phe | Ser | Leu | Asp | Thr | Ser | Lys | Ser | Thr | Ala | Tyr |
| 65 | | | | | 70 | | | | | 75 | | | | 80 | |
| Leu | Gln | Met | Asn | Ser | Leu | Arg | Ala | Glu | Asp | Thr | Ala | Val | Tyr | Tyr | Cys |
| | | | 85 | | | | | | 90 | | | | | 95 | |
| Ala | Arg | Gly | Tyr | Arg | Ser | Tyr | Ala | Met | Asp | Tyr | Trp | Gly | Gln | Gly | Thr |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Leu | Val | Thr | Val | Ser | Ser | Ala | Ser | Thr | Lys | Gly | Pro | Ser | Val | Phe | Pro |
| | | | 115 | | | | 120 | | | | | 125 | | | |
| Leu | Ala | Pro | Ser | Ser | Lys | Ser | Thr | Ser | Gly | Gly | Thr | Ala | Ala | Leu | Gly |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Cys | Leu | Val | Lys | Asp | Tyr | Phe | Pro | Glu | Pro | Val | Thr | Val | Ser | Trp | Asn |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
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Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220
His Thr Cys Ala Ala
225

<210> 116
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<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic CDP870 nucleic acid sequence (sense strand)

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<210> 117
<211> 1477
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic CDP870 nucleic acid sequence (anti-sense strand)

<400> 117

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